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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/616,409 | 07/09/2003 | Sharlene Adams | I0248.70024US00 | 9289 |

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Maria A. Trevisan
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

| EXAMINER | |
|---|---|
| FETTEROLF, BRANDON J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 07/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/616,409 | ADAMS ET AL. | |
| | Examiner | Art Unit | |
| | Brandon J. Fetterolf, PhD | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,7-17,139,142,144,166,251-260,338 and 340-347* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 7-17, 139, 142, 144, 166, 251-260, 338 and 340-347* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

### *Response to the Amendment*

The Amendment filed on 04/27/2006 in response to the previous Non-Final Office Action (10/21/2005) is acknowledged and has been entered.

Claims 1-3, 7-17, 139, 142, 144, 166, 251-260, 338 and new claims 340-347 are currently pending and under consideration.

The Declaration's Under CFR 1.132 filed on 4/27/2006 by Dr. Barry Jones and Dr. Margaret J. Uprichard is acknowledged and has been considered.

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

**All rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.**

**New Objections Necessitated by Amendment:**

### *Claim Objections*

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, it is unclear how the recitation in claim 3 that the anti-CD20 antibody or antibody fragment is an antibody further limits the anti-CD20 antibody or fragment thereof already set forth in claim 1.

**New Rejections Necessitated by Amendment:**

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Dependent claim 3 has been amended to recite the limitation of "wherein antibody dependent cell-mediated cytotoxicity is enhanced." However, while the claims as originally filed supports stimulating an immune response in a subject, wherein the immune response is antibody dependent cell-mediated cytotoxicity, a careful review of the specification, as originally filed, does not appear to lend support for the limitation that the antibody dependent cell-mediated cytotoxicity is enhanced. Emphasis in the instant situation is on the term "enhanced" which would infer that the action of an anti-CD20 antibody, e.g., inhibition of tumor growth, is more than that alone. Thus, while the specification (figure 3) appears to suggest that the combination of PT-100 and rituximab has a greater growth inhibitory effect against a tumor than either treatment by itself, it cannot be determined if the result is an enhancement of anti-CD20's antibody dependent cell-mediated cytotoxicity or whether a result of the additive effect of the combination because the specification (figure 2) also teaches that PT-100 has growth inhibitory effects. Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06

## *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 8-17, 139, 144, 166, 251-260, 338 and 340-347 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaminski et al. (US 6,090365, 2000) as evidenced by Ajay et al. (Proc. Am. Soc. Clin. Oncol. 2001; 20: Abstr 1118) in view of Wallner et al. (WO 00/71135, 2000, IDS).

Kaminski et al. teach a method of treating a lymphoma in a patient comprising administering a therapeutic dose of a radiolabelled anti-CD20 antibody, wherein the radiometric dose received by the patient is limited to a level that toxicity to bone marrow is not significant and reconstitution of hematopoietic function, by bone marrow transplantation or by other means, is not required (column 5, lines 45-53). With regards to the administration, the patent teaches that the anti-CD20 antibodies can be administered by intravenous injection or intralymphatic injection (column 10, lines 8-24). In addition to treating lymphoma's, the patent also teaches that the method can be applied to the treatment of a variety of leukemia's such as hairy cell leukemia and chronic myeloblastic leukemia's (column 6, lines 10-19). Moreover, the patent teaches that the method of treatment is amendable to the treatment of chronic diseases or diseases that have relapsed after a period of remission (column 6, lines 20-24). Thus, while Kaminski et al. does not specifically teach that the radiolabelled anti-CD20 antibody is tositumomab, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art disclosure because as evidenced by Ajay et al., tositumomab is available through Coulter Pharmaceuticals the assignee of the US 6,090,365 patent. Thus, the claimed antibody appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product

of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Kaminski et al. does not explicitly teach a method of enhancing treatment with an anti-CD20 antibody or a fragment thereof in a subject having cancer comprising administering an agent of Formula I and an anti-CD20 antibody or a fragment thereof.

Wallner et al teach (abstract) a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II as shown in the specification on page 25, wherein formula II is a cyclic derivative. With regards to the agent of Formula I, the WO document teaches that the agent comprises the formula PR, wherein P is a targeting group which binds to the reactive site of post praline-cleaving enzyme, and R is a reactive group capable of reacting with a functional group in a post proline cleaving enzyme (page 8, lines 12-14). Specifically, the reference teaches (page 2, line 25 to page 3, line 17) that the agent is Val-boro-Pro, wherein the agent may be a racemic mixture of the D/L isomers or may be the all L-isomer. Wallner et al. further teaches (page 43, lines 17+ and Figure 1) that IL-6 levels were increased upon the addition of the agent to Fischer D+ rat and BM stromal cells. Moreover, Wallner et al. disclose (page 22, lines 6-9, 27-28 and page 25, line 23) that the method may further comprise administering the agent in combination with existing therapies for cancer such as the use of monoclonal antibodies and/or localization radiation, wherein the efficacy of the existing therapy is improved. With regards to the administration, the WO document teaches (page 22, lines 11-13 and page 27, lines 28-29) that the agents may be administered prior to, concurrent with, or following the existing therapy. Specifically, the WO document teaches (page 28, lines 24-27) that if the existing cancer is a monoclonal antibody, the treatment can performed at sub-lethal dose. The reference further teaches that the agent may be administered to those patients who may have been immunosuppressed (reduction in lymphoid cells) such as in a patient treated for lymphoma, provided that at the time the treatment the subject has protective or normal levels of hemopoeitic cells (page 20, lines 37-30). In addition to those patients suffering from cancer, Wallner et al. teach that the subject may be HIV negative (page 3, line 27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat cancer. In the instant case, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). As such, one of skill in the art would have been motivated to do so because Wallner et al. teach that the boroproline derivatives when used in combination with an existing therapy such as localization radiation (e.g., radioimmunotherapy of cancer) are useful in improving the efficacy of the existing therapies for treating conditions such as cancer. Thus, one of ordinary skill in the art would have reasonably expectation that by administering a compound of formula I or II in combination with the radiolabelled anti-CD20 antibody as taught by Kaminski et al., one would achieve a method of enhancing the efficacy of the radiolabelled anti-CD20 antibody.

Moreover, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the administration times and/or routes of administration of the antibody and the compound of Formula I. One would have been motivated to do so because the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results, see In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) or In re Gibson, 39 F.2d 975. Thus, one would have a reasonable expectation that the administration of the antibody simultaneously, sequentially or prior to the administration of the second therapeutic agent would result in the treatment of a tumor.

Claims 1-2, 7-17, 139, 144, 251-260 and 338 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 5,776,456, 1998) as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9) in view of Wallner et al. (WO 00/71135, 2000, IDS).

Anderson et al. teach a method of treating lymphoma comprising administering an immunologically active anti-CD20 antibody, radiolabeled anti-CD20 antibody or a combination of an anti-CD20 antibody and radiolabeled anti-CD20 antibody (abstract). With regards to the administration of the anti-CD20 antibody, the patent teaches that the anti-CD20 antibodies and radiolabeled antibodies are administered by intravenous, intramuscular, subcutaneous or

intraperitoneal routes (column 7, lines 55-61). Moreover, the patent teaches that depletion levels of peripheral blood B lymphocytes was maintained for up to 7 days; after this period, B cell recovery began (column 25, lines 59-64). Thus, while Anderson et al. does not specifically teach that the anti-CD20 antibody is rituximab, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art disclosure because as evidenced by Grillo-Lopez et al, rituximab is clinically developed by IDEC Pharmaceutical Corporation which is the assignee of the US 5,776,456 patent. Thus, the claimed antibody appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Anderson et al. does not explicitly teach a method of enhancing treatment with an anti-CD20 antibody or a fragment thereof in a subject having cancer comprising administering an agent of Formula I and an anti-CD20 antibody or a fragment thereof.

Wallner et al teach (abstract) a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II as shown in the specification on page 25, wherein formula II is a cyclic derivative. With regards to the agent of Formula I, the WO document teaches that the agent comprises the formula PR, wherein P is a targeting group which binds to the reactive site of post praline-cleaving enzyme, and R is a reactive group capable of reacting with a functional group in a post proline cleaving enzyme (page 8, lines 12-14). Specifically, the reference teaches (page 2, line 25 to page 3, line 17) that the agent is Val-boro-Pro, wherein the agent may be a racemic mixture of the D/L isomers or may be the all L-isomer. Wallner et al. further teaches (page 43, lines 17+ and Figure 1) that IL-6 levels were increased upon the addition of the agent to Fischer D+ rat and BM stromal cells. Moreover, Wallner et al. disclose (page 22, lines 6-9, 27-28 and page 25, line 23) that the method may further comprise administering the agent in combination with existing therapies for cancer such as the use of monoclonal antibodies and/or localization radiation, wherein the efficacy of the existing therapy is improved. With regards to the

administration, the WO document teaches (page 22, lines 11-13 and page 27, lines 28-29) that the agents may be administered prior to, concurrent with, or following the existing therapy. Specifically, the WO document teaches (page 28, lines 24-27) that if the existing cancer is a monoclonal antibody, the treatment can be performed at sub-lethal dose. The reference further teaches that the agent may be administered to those patients who may have been immunosuppressed (reduction in lymphoid cells) such as in a patient treated for lymphoma, provided that at the time the treatment the subject has protective or normal levels of hemopoeitic cells (page 20, lines 37-30). In addition to those patients suffering from cancer, Wallner et al. teach that the subject may be HIV negative (page 3, line 27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat cancer. In the instant case, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). As such, one of skill in the art would have been motivated to combine the references because Wallner et al. teach that the boroproline derivatives when used in combination with an existing therapy such as localization radiation (e.g., radioimmunotherapy of cancer) are useful for improving the efficacy of the existing therapies for treating conditions such as cancer. Thus, one of ordinary skill in the art would have reasonably expectation that by administering a compound of formula I or II in combination with the an antiCD20 antibody or radiolabelled anti-CD20 antibody as taught by Anderson et al., one would achieve a method of enhancing the efficacy of the existing anti-CD20 therapy.

Moreover, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the administration times and/or routes of administration of the antibody and the compound of Formula I. One would have been motivated to do so because as taught by Wallner et al. the boroproline derivatives can be used for the treatment of patients who may been myelosuppressed or immunosuppressed, provided that at the time of treatment the subject has protective levels of hemopoeitic cells, whereas Anderson et al. teach that normal levels of lymphatic cells after 7 days post anti-CD20 infusion. As such, the selection of any order of

performing process steps is *prima facie* obvious in the absence of new or unexpected results, see In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) or In re Gibson, 39 F.2d 975. Thus, one would have a reasonable expectation that the administration of the antibody prior to or after the administration of the second therapeutic agent would result in the treatment of B-cell lymphoma.

Claims 340-347are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 5,776,456, 1998) as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9) in view of Wallner et al. (WO 00/71135, 2000, IDS) in further view of Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9).

Anderson et al. in view of Wallner et al. teach, as applied to claims 1-2, 7-17, 139, 144, 251-260 and 338), a method of treating B-cell lymphoma comprising administering an immunologically effective amount of an anti-CD20 antibody in combination with a boroproline derivative.

The combination of Anderson et al. in view of Wallner et al. does not explicitly teach that the b-cell lymphoma is Non-Hodgkin's lymphoma or a refractory form of Non-Hodgkin's lymphoma.

Grillo-Lopez et al. disclose that rituximab has been approved by the FDA for the treatment of relapsed or refractory, CD20 positive, B-cell, low-grade or follicular non-Hodgkin's lymphoma.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat Non-Hodgkin's lymphoma or refractory non-Hodgkin's lymphoma. One would have been motivated to do so because as taught by Grillo-Lopez et al., rituximab has already been taught in the prior art and approved by the FDA for the treatment of non-Hodgkin's lymphoma and refractory non-Hodgkin's lymphoma. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient suffering from non-Hodgkin's lymphoma or refractory non-Hodgkin's lymphoma the combination as taught by Anderson et al and Wallner et al., one would achieve method of enhancing the efficacy of the existing anti-CD20 therapy for non-Hodgkin's lymphoma or refractory non-Hodgkin's lymphoma.

Claim 142 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kaminski et al. (US 6,090365, 2000) as evidenced by Ajay et al. (Proc. Am. Soc. Clin. Oncol. 2001; 20: Abstr 1118) in

view of Wallner et al. (WO 00/71135, 2000, IDS) and in further view of Buske et al. (European Journal of Cancer 1999; 35: 549-557).

Kaminski et al in view of Wallner et al. teach, as applied to claims 1-2, 8-17, 139, 144, 166, 251-260, 338 and 340-347 above, a method of enhancing treatment with an anti-CD20 antibody or a fragment thereof in a subject having a lymphoma comprising administering a radiolabelled anti-CD20 antibody in combination with a therapeutically effective amount of a boroproline derivative. In addition to the treatment of lymphoma with a radiolabelled CD20 antibody alone, Kaminski et al. teach the treatment of lymphoma using a combination of anti-CD20 antibodies and radiolabelled antibodies (column 5, lines 54-60).

The combination of Kaminski et al. in view of Wallner et al. do not explicitly teach that an anti-CD20 antibody conjugated to a toxin.

Buske et al. disclose the emerging concepts monoclonal antibody therapy for B-cell non-Hodgkin's lymphomas. Specifically, the reference teaches that the cytolytic activity of the native Mab can be enhanced by coupling an antibody with a plant or bacterial toxin (page 551, 1st column, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conjugate a bacterial toxin or plant toxin to the anti-CD20 antibody as taught by Kaminski et al. in view of the teachings of Buske et al. One would have been motivated to do so because as taught by Buske et al., conjugation of a plant or bacterial toxin enhances the cytolyitic activity of the Mab. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by conjugating a plant or bacterial toxin to an anti-CD20 antibody, one would achieve a method of enhancing the therapeutic effect of the anti-CD20 antibody on B-cell mediated non-Hodgkin's lymphoma.

Claim 142 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 5,776,456, 1998) as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology 2000; 1: 1-9) in view of Wallner et al. (WO 00/71135, 2000, IDS) and in further view of Buske et al. (European Journal of Cancer 1999; 35: 549-557).

Anderson et al. in view of Wallner et al. teach, as applied to claims 1-2, 7-17, 139, 144, 251-260 and 338), a method of treating B-cell lymphoma comprising administering an immunologically

effective amount of an anti-CD20 antibody in combination with a boroproline derivative. Specifically, Anderson et al. teach a method of treating lymphoma comprising administering an immunologically active anti-CD20 antibody, radiolabeled anti-CD20 antibody or a combination of an anti-CD20 antibody and radiolabeled anti-CD20 antibody (abstract).

The combination of Anderson et al. in view of Wallner et al. does not explicitly teach that the anti-CD20 antibody is conjugated to a toxin such as a plant or bacterial toxin.

Buske et al. disclose the emerging concepts monoclonal antibody therapy for B-cell non-Hodgkin's lymphomas. Specifically, the reference teaches that the cytolytic activity of the native Mab can be enhanced by coupling an antibody with a plant or bacterial toxin (page 551, 1st column, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conjugate a bacterial toxin or plant toxin to the anti-CD20 antibody as taught by Anderson. in view of the teachings of Buske et al. One would have been motivated to do so because as taught by Buske et al., conjugation of a plant or bacterial toxin enhances the cytolyitic activity of the Mab. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by conjugating a plant or bacterial toxin to an anti-CD20 antibody, one would achieve a method of enhancing the therapeutic effect of the anti-CD20 antibody on B-cell mediated non-Hodgkin's lymphoma.

Therefore, NO claim is allowed

## *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

BF
July 5, 2006